Please add the following new claim:

--53. A method of identifying a mammalian cell containing a mutant Rad51 gene comprising determining the sequence of all or part of an endogenous Rad51 gene of a mammalian cell and comparing said sequence to a known mammalian Rad51 gene sequence of the same mammalian species as said cell, wherein a difference in the sequence between the Rad51 gene of said individual and said known Rad51 gene is indicative of a disease state or a propensity for a disease state.--

REMARKS

Claims 18, 19, 21, and 47-52 are pending. Claims 18, 19, 21, and 47-52 stand rejected under 35 U.S.C. § 112, first paragraph as lacking an enabling disclosure; Claims 51 and 52 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite; and Claim 18 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Ogawa, *et al.*, *RecA-like Recombination Proteins in Eukaryotes: Functions and Structures of Rad51 Genes*, Cold Harbor Symposium on Quantitative Biology, 43:567-576 (1993) ("Ogawa *et al.*").

Claims 18, 21, and 47-52 have been amended to recite with more particularity that which Applicants regard as their invention. Claim 53 is newly added with the present amendment.

Support for the amendments to Table 9 (53:7, and 53:11) can be found in U.S. Provisional Application Serial Number 60/045,668, filed May 6, 1997 ('668 Application), from which the instant application claims priority, and which is expressly incorporated by reference in the instant application (1:2-3). Table 9 of the instant application corresponds to Table 4 (page 31) of the '668 Application; page 31 is attached hereto for the Examiner's convenience. The Examiner will recognize that the second occurrence of 45% at 53:7 was a typographical error and should be 9% as indicated in Table 4 of the '668 Application.

Support for the amendments and new claim can be found throughout the specification and in the originally filed claims. No claims have been canceled. The amendments and new claim present no new matter, and entry thereof is respectfully requested. A copy of the pending claims is attached hereto for the Examiner's convenience.

The Invention

Despite the significant investigation of Rad51 activity prior to the present invention, there was no demonstrated correlation between Rad51 activity and any disease states. The present invention relates to the discovery that such correlation exists between several disease states and aberrant Rad51 behavior. More specifically, the eludication of this correlation leads to the examination of genes that encode Rad51, and for mutations that result in the aberrant Rad51 behavior in these disease states.

It is known that mutations of the p53 gene exist in a large percentage of known cancers. It is also known that Rad51 and p53 can interact on a protein level and have somewhat similar biochemical functions. Therefore, it is believed that the correlation of the present invention between aberrant Rad51 activity and several disease states, in combination with the overwhelming relationship of mutations in the p53 gene to cancer, the interactions of p53 and Rad51 on a protein level, and the similar biochemical functions of the two molecules, suggests that variant Rad51, or incorrectly controlled Rad51 levels may be important in any disease states correlated with atypical Rad51 activity.

Thus, one embodiment of the present invention is a method for identifying mutations present in a mammalian Rad51 gene. Another embodiment of the present invention is a method of identifying mutations present in a mammalian Rad51 gene, wherein the mutation is responsible for aberrant Rad51 activity in a disease state, or alternatively the mutation indicates a disease state exists, or a propensity that a disease state exists.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 18, 19, 21, and 47-52 stand rejected under 35 U.S.C. § 112, first paragraph as lacking an enabling disclosure.

Claim 18 requires, *inter alia*, determining a sequence of all or part of an endogenous Rad51 gene, and comparing the sequence with all or part of the sequence from a wild-type Rad51 gene, thereby determining whether the endogenous Rad51 gene is mutated as compared to the wild-type Rad51 gene.

The Examiner first argues that Claim 18 is lacks any utility other than diagnostics because this is the only utility identified by the specification and no other utility for the

claimed invention is recognized within the art. Additionally, the Examiner argues that a skilled artisan must identify a specific mutation in a Rad51 gene associated with a disease state in order to use the claimed invention for diagnostics. The Examiner concludes that for the skilled artisan to identify specific mutations in a Rad51 gene would require undue experimentation, and thus the specification does not enable the claimed invention.

The Examiner's rejection falls in the class of 35 U.S.C. § 112, first paragraph lack of enablement rejections that is related to a 35 U.S.C. § 101 lack of utility rejection, the latter of which the Examiner has not made in the present case. *See, e.g., In re Cortright* 49 USPQ2d 1464, 1466 (Fed. Cir. 1999) (enablement rejection takes several forms); *In re Brana*, 34 USPQ2d 1436, n16 (Fed. Cir. 1995) (rejection under section 112, first paragraph that specification failed to convince the skilled artisan that claimed compounds are useful appears to be section 101 issue, rather than section 112 issue). Section 101 utility and section 112, first paragraph enablement rejections are related in that it logically follows that a specification cannot teach the skilled artisan "how to use" something that lacks utility.

To make this type of section 112, first paragraph rejection, the Examiner has the burden of challenging a "presumptively correct assertion of utility in the disclosure." *In re Brana*, 34 USPQ2d at 1441; *In re Cortright*, 49 USPQ2d at 1466 (*citing In re Brana*). To meet this burden, the Examiner must have "reason to doubt the objective truth of the statements [of utility] contained in the written description." *In re Cortright*, 49 USPQ2d at 1466. A written description that "'suggest[s] an inherently unbelievable undertaking or involve[s] implausible scientific principles'" is one way in which the Examiner may establish a reason to doubt an asserted utility for an invention. *Id.* (*quoting In re Brana*, 34 USPQ2d at 1441) (other citations omitted). It is respectfully submitted that the Examiner has not met his burden.

Claim 18 recites a method for identifying a mammalian cell containing a mutant Rad51 gene. The specification provides several working examples that establish a correlation between aberrant Rad51 activity and several disease states. It is known that Rad51 interacts on a protein level with p53, BRCA1, BRCA2, and possibly with the RNA polymerase II complex. Vispé *et al.*, Mammalian Rad51 Protein: A RecA Homologue With Pleiotropic Functions, Biochimie 79:587-592 (1997) ("Vispé *et al.*") (cited by the Examiner). It is also

known that mutations in p53 exist in a large number of known cancers, and that mutations in BRCA1 and BRCA2 have been linked to predisposition for breast and ovarian cancers. *Id.* Therefore, as expressly identified in the present specification, the correlation between aberrant Rad51 activity and several disease states, in combination with the overwhelming relationship of mutations in the p53 gene to cancer, the interactions of Rad51 with p53, BRCA1, BRCA2 and polymerase II complex on a protein level, and the similar biochemical functions of Rad51 and p53, suggests that variant Rad51, or incorrectly controlled Rad51 levels may be important in any disease states correlated with aberrant Rad51 activity. A skilled artisan, in light of the present disclosure, would clearly find it useful to identify cells containing a mutant Rad51 gene, beyond merely diagnosing the cell for a disease state as urged by the Examiner. As will be readily appreciated by the skilled artisan, it would be useful to identify cells with mutant Rad51 genes for a variety of purposes, including the elucidation of a disease mechanism, pharmaceutical development or gene therapies, to mention a few.

The Examiner has not indicated any reason to doubt the objective truth of the usefulness identified within the written description and well understood by the skilled artisan. *In re Cortright*, 49 USPQ2d at 1466. Moreover, the usefulness of the present invention does not suggest an inherently unbelievable undertaking or involve implausible scientific principles. *Id.* It is respectfully submitted that the Examiner has not established a *prima facie* case that the specification fails to teach the skilled artisan "how to use" the present invention.

Furthermore, there is no doubt that one skilled in the art has the tools and know how to determine sequences of a Rad51 gene and compare the sequences with a known sequence of a Rad51 gene to identify mutations. The Examiner urges that a skilled artisan must identify a specific mutation associated with a disease state to practice the invention. However, nothing in the claimed invention requires such an identification to practice the invention. Rather, this limitation is improperly read into the claims by the Examiner.

Applicant respectfully submits that the specification provides ample guidance on "how to use" the claimed invention without undue experimentation. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph of Claims 18, 19, 21, and 47-52 be withdrawn.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 51 and 52 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite because the limitation "the mutation in Rad51" lacked antecedent basis. Claims 51 and 52 have been amended to obviate this rejection. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 102(b)

Claim 18 stands rejected under 35 U.S.C. § 102(b) as anticipated by Ogawa, *et al.*

An anticipation rejection requires that a single reference expressly or inherently disclose each and every element of a claim. *In re Paulsen*, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994); MPEP § 2131 (citing *Richardson v. Suzuki Motor Co.* , 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claim 18, as amended, recites a method of identifying a mammalian cell containing a mutant Rad51 gene, by comparing at least a part of an endogenous mammalian gene to a known mammalian Rad51 gene of the same species. Ogawa *et al.* does not compare gene sequences of Rad51 from the same species, and does not identify a mutation of the Rad51 gene. Therefore, Ogawa *et al.* do not disclose each and every element of the claimed invention.

Ogawa *et al.* do not anticipate the claimed invention. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §102(b) of Claim 18 be withdrawn.

CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and an early notification of such is solicited. If, upon review, the Examiner feels there are additional outstanding issues, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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Table 4. Rad51 Foci and Apoptosis in Colcemid-Induced Micronuclei of TGR-1 Cells

Treatment	Number of micro-nuclei in 1000 cells	Percentage of Cells Showing [a]			
		Rad51-/ FISEL-	Rad51+/ FISEL-	Rad51+/ FISEL+	Rad51-/ FISEL+
None	93	75%	12%	2%	11%
Colcemid [b]	n.d.	85%	6%	0%	9%
1 day of recovery	1293	54%	31%	1%	14%
2 days of recovery	1061	45%	9%	6%	40%
3 days of recovery	769	43%	7%	4%	46%

[a] Apoptotic cells show fluorescence in situ end labeling (FISEL+), while cells without genome fragmentation show absence of labeling (FISEL-). "Rad51+" cells with Rad51 foci, "Rad51-" cells without foci.

[b] TGR-1 cells were grown for 24 hrs in medium containing 0.1 μg/ml colcemid to induce micronucleus formation (without inducing DNA damage). 18% of the colcemid-treated cells were arrested at metaphase, 17% showed multinuclei (>10 micronuclei), and 65% had no micronuclei. The cells were then allowed to recover for various times in the absence of the drug. 500 micronuclei were analyzed for each experiment.